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Case report

Primary angiosarcoma of the breast complicated by the syndrome of disseminated intravascular coagulation (DIC): Case report and literature review

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ABSTRACT

Primary angiosarcoma of the breast (PAB) accounts for 0.04% of all breast malignant tumors. It affects young women usually at third or fourth decades of life. PAB clinically manifests as a painless, movable mass with sharp limits. A bluish red discoloration of the overlying skin is often observed. Enlargement of axillary lymph nodes generally does not occur.

Angiosarcoma of the breast has a very poor prognosis due to the tendency to metastasize haematogenously and high frequency of local recurrence.

Mastectomy and chemotherapy are preferable treatment choices.

This paper presents a case of primary angiosarcoma of the breast with a syndrome of disseminated intravascular coagulation (DIC).

1. Background

Primary angiosarcoma of the breast (PAB) is a rare and extremely aggressive neoplasm of the endovascular origin. Two hundred and nineteen cases have been documented[1] since the first case reported by Schmidt in 1887.[2] Both Schmidt and later Borrmann in 1907 described this condition as lethal.[9] The incidence rate of this tumor has remained relatively constant, accounting for 0.04% of all breast tumors.[4] and approximately 8% of mammary sarcomas.[5] Several terms have been used to describe this malignant condition such as hemangioendothelioma,[3] haemangioblastoma,[6] hemangiosarcoma[7,8] and metastasizing angioma.[9–11]

The usual clinical presentation of angiosarcoma is a painless smooth mass, but in approximately 17% of cases the tumor may appear with red discoloration and apparent bruising of the overlying skin.[12] PAB carries very poor prognosis with a five-year survival rate of 8–50%.[13] The mean latency ranges from 5 to 6 years. Distant metastases have been observed in the lungs, skin, liver, bones, CNS, spleen, ovary, lymph nodes and heart.[14,15] The angiosarcoma may relapse in the same breast especially after conservative surgery and postoperative radiation.[16]

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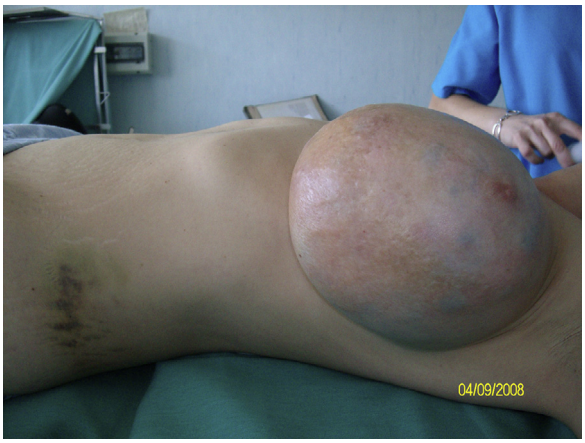

Fig. 1 – A bluish red discoloration of the overlying skin of the breast and in the middle of the abdominal region.

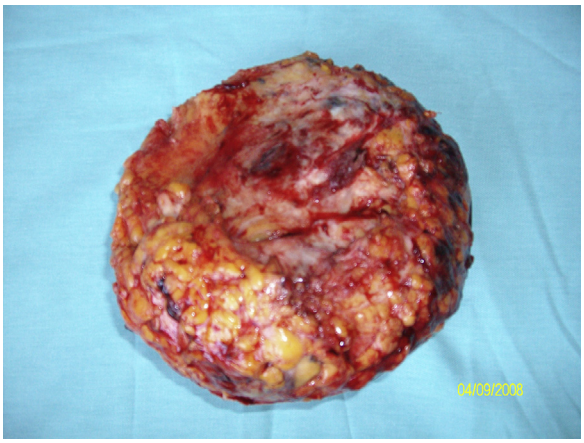

Fig. 2 – Completely surgically excised tumor.

We report an uncommon clinical case of an advanced breast angiosarcoma, without distant metastases, but associated with disseminated intravascular coagulation (DIC) by consumption coagulopathy, known as the Kasbach–Merritt syndrome.

2. Case report

The patient was a 42-year-old woman who had a tumor in the left breast for three years. During this period the patient refused any treatment for her disease and no such treatment was done. In the last two months, before the current hospitalization, the tumor rapidly grew and the overlying skin colored in red. The patient was admitted to the National Cancer Center Sofia on August 2, 2007, in a critical condition. The physical examination revealed a hard, mobile, painless mass located in the central region of the left breast. On palpation the tumor dimensions were 18/16/14 cm and had sharp limits. No enlargement of axillary lymph nodes, no nipple retraction and no skin thickening were found. The right breast was normal. The overlying skin of the affected one had bluish red discoloration (Fig. 1). Similar red discoloration was seen on other parts of the body such as the back, the legs and the middle of the abdominal region (Fig. 1). X-ray mammography of the left breast showed a big tumor mass of 18.5 cm in diameter, without spiculae or microcalcifications. Ultrasound showed a liquid area in the central zone of the tumor. The tumor marker CA15-3 was within the referenced limits. Distant metastases were not established. On admission, the coagulation tests showed exhausted haemostatic potential with low platelet count, no detectable fibrinogen and no coagulation of APTT and PT. There were high levels of D-dimmers. These laboratory findings, together with the clinically manifested bleeding diathesis with big suffusions on the skin in the sites of venepunctures, were interpreted to be caused by disseminated intravascular coagulation (Table 1). D-dimers were measured using commercial antibody-based assay.

Substitution therapy was performed with 7 units of platelet concentrate, 10 ml/kg fresh frozen plasma and 2 units of red blood cell concentrate. The response to the therapy was highly satisfactory. Platelet counts reached 70×10^9/l, fibrinogen increased to 3.5 g/l and APPT and PT were normalized. The surgery was performed with no excessive bleeding. The normal range of platelets was reached on the next day after surgery with no additional substitution therapy (Table 1). The tumor was completely excised en bloc with the first level axillary lymph nodes due to their being visibly enlarged (Fig. 2).

The mastectomy specimen showed bruising of the skin and a well-defined tumor. The cut surface of the tumor was soft, spongy, bluish, hemangioma-like, with necroses and hemorrhages as results of numerous dilated blood vessels (Fig. 3).

Microscopic examination of the tumor revealed a mixed structure – it contained areas of endothelial tufting with papillary formation and solid spindle cell components, corresponding to poorly differentiated angiosarcoma – Grade 3 (Fig. 4). Hemorrhages, necroses, cellular pleomorphisms and mitotic figures were also observed. By means of immunocytochemistry, endothelial marker CD 31 was used, and it strongly stained the sarcoma cells (Fig. 5).

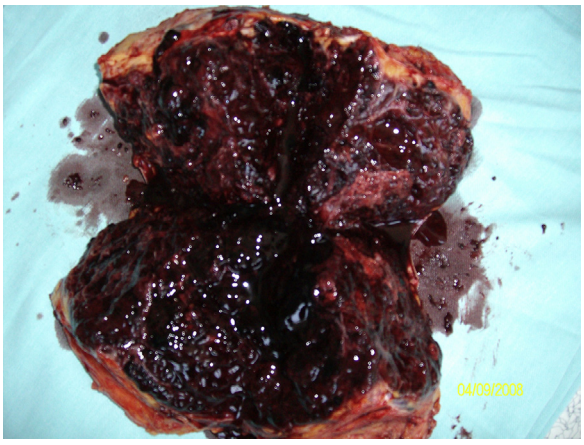

Fig. 3 – Necrosis and hemorrhages in the central tumor area.

Table 1 – Coagulation status of the patients before and after therapy.

Date	Platelets	Fibrinogen	APTT	PT	D-dimers
29.08.2008	28×10^9/l	–	157 secunds	12% activity	–
01.09.2008	50×10^9/l	Not detectable	No coagulation	No coagulation	>2000 ng/ml
02.09.2008	50×10^9/l	Not detectable	51.5 secunds	No coagulation	–
Transfusion therapy: Fresh frozen plasma 10 ml/kg					
03.09.2008	35×10^9/l	0.69 g/l	47.8 secunds	42% activity	–
Transfusion therapy: Platelet concentrates 7 U; Red blood cells concentrate 2 U					
04.09.2008	70×10^9/l	3.5 g/l	35.7 secunds	78% activity	–
Surgery on 04.09.2008					
05.09.2008	120×10^9/l	–	–	–	–

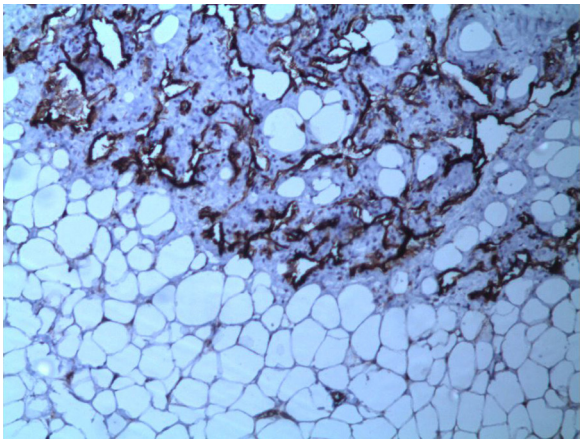

Fig. 4 – Primary angiosarcoma of the breast in a 42-year old woman, HE stain, orig. magnification on ×250: areas of endothelial tufting with papillary formation and solid spindle cell components.

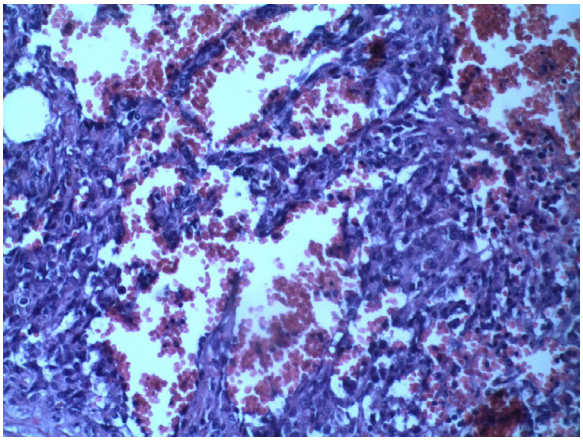

Fig. 5 – Angiosarcoma cells stained strongly for CD31, immunoperoxidase labeling, orig. magnification ×250.

3. Discussion

Primary angiosarcoma of the breast is an uncommon neoplasm with unknown etiology. Some authors have reported one angiosarcoma in every 1700–2300 cases of breast cancer.[17,18]

Angiosarcoma occurs almost exclusively in the female breast, with only five cases of male breast angiosarcoma being documented.[19] PAB affects primarily young women in their thirties and forties, unlike breast carcinoma, which usually arises later on in life.[20]

Breast angiosarcoma usually manifests as a palpable, painless mass, moderately mobile within the surrounding tissue. The tumor may have either ill-defined or sharply circumscribed borders. Sometimes the disease may have a covert, insidious clinical course, manifesting as a discrete mass that grows rapidly, as in the case of our patient.[12] Less often (in approximately 2% of all cases), angiosarcoma may appear as a diffusive enlargement of the breast. In most cases there is no nipple retraction, discharge or axillary lympadenopathy. However, a bluish red discoloration of the overlying skin is a frequent symptom, as was also observed in this case. Tumor size usually exceeds 4 cm in diameter.[15] Here we describe a locally advanced tumor of 18.5 cm in diameter.

Mammography is the standard imaging approach for diagnostic information. Breast X-rays may appear completely normal in about 33% of cases.[21] On mammograms, angiosarcoma appears to be a tumor mass without spiculation, microcalcification or enlargement of the regional lymph nodes. In our patient the mammographic findings were nonspecific. Many other authors also reported normal mammographic findings.[22]

Magnetic resonance imaging of angiosarcoma shows a mass with low signal intensity on T1-weighted images. Histological slides demonstrate dilated channels and vascular spaces filled with slowly flowing blood.[23]

Preoperative diagnosis by means of aspiration cytology and biopsy is tricky and often gives falsely negative results. Chen et al. reported that the false negative rate was 37%.[14] Therefore, immune histological staining for factor 8-related antigens is usually beneficial to the diagnosis.[24]

The patient's worsening condition and probability of the threat of bleeding prevented us from applying other diagnostic tools, such as fine needle biopsy and magnetic resonance. In patients with cancer, the pathogenic mechanism of hematologic disorders such as DIC is not clearly understood. From the clinical viewpoint, most cases of cancer-associated hematologic disorders have been reported in patients with gastric and breast cancer.[24–26]

DIC represents the result of a widespread activation of the coagulation pathway.[27] DIC proceeds from the simultaneous occurrence of systemic fibrin formation resulting from an increased generation of thrombi, impaired physiological

anticoagulation mechanism, and inadequate fibrinolysis. The combination of increased formation and impaired removal of fibrin results in thrombotic occlusion of small and medium sized vessels. In cancer patients, tumor cells express a variety of procoagulant molecules including tissue factor and cancer procoagulant, which activate the host's hemostatic system.[28,29] Tumor cells also express fibrinolytic inhibitors such as plasminogen activator type 1, creating the hypofibrinolytic state that is characteristic of DIC.[30] Proinflammatory cytokines, such as tumor necrosis factor α and interleukin-6, are also involved in DIC development.[31,32]

Kasabach–Merritt syndrome (KMS) is defined by a huge haemangioma with thrombocytopenia and consumption coagulopathy.[33] Endothelial defects within the haemangioma cause platelet activation, thrombosis formation, consumption of coagulation factors, and increased fibrinolysis because of localized intravascular coagulation.[34] Studies using radiolabeled fibrinogen and platelets have provided evidence that within the hemangioma, tere occurs the consumption of platelets and fibrinogen.[35] Kasabach–Merritt syndrome was originally described in benign haemangioma. We observed the same process in a malignant tumor of endothelial origin and cavernous space in it. Since the rate of consumption of the coagulation potential was of a low grade, it was corrected with limited amount of platelets and fresh frozen plasma.

Concerning the possible mechanism of the coagulation disorder two possibilities may be discussed:

1. Despite the malignant origin of the tumor, the activation of coagulation was most probably only local and did not engage the complex mechanisms of DIC associated with malignancy.
2. There was a combination of these two possible mechanisms in a low grade.

Due to the unknown etiological factors of this rare malignancy, there is no established standard treatment. Mastectomy is treatment of choice, in some cases breast conserving surgery may also be considered. Complete surgical excision is found to be better than what is generally believed. Adjuvant chemotherapy is often carried out on patients with primary breast angiosarcoma and distant metastases, but the results are unsatisfactory.[12,15,36]

Recently, a new treatment approach has been investigated. Endoglin is an antigen that is found mainly on the surface of endothelial cells.[37] Thorpe et al. suggested that it may be possible to treat angiosarcoma with anti-endoglin monoclonal antibodies if immunohistochemical staining is positive for endoglin.[38] Their assumptions are based on the close interaction between endothelial cells and the blood. This makes vasculature a practical target for therapy.

Prognosis of angiosarcoma is thought to depend on the histological grade.[39] Patients with higher grade lesions are more prone to higher rates of local recurrences and have a lower survival rate.[18,21] In our patient the tumor was found to be of a relatively high grade, and subsequently she was referred to adjuvant therapy. Poor prognosis of breast angiosarcoma is associated also with a tendency to metastasize hematogenously.[23]

Conflict of interest

None declared.

Financial disclosure

None declared.

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